IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF ARKANSAS
WESTERN DIVISION

In re:	§	**MDL Docket No. 4:03CV1507WRW**
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PREMPRO PRODUCTS LIABILITY	§	**Reeves v. Wyeth, 4:05CV00163WRW**
LITIGATION	§	**Rush v. Wyeth, 4:05CV00497 WRW**
	§	

PLAINTIFFS' MEMORANDUM IN OPPOSITION TO DEFENDANTS' MOTION TO EXCLUDE EXPERT TESTIMONY OF DR. DONALD AUSTIN

Les Weisbrod, Esq.
MORGAN & WEISBROD
11551 Forest Central Dr., Suite 300
P.O. Box 821329
Dallas, TX 75243
Tel: (214) 373-3761
Fax: (214) 739-4732

William B. Curtis, Esq.
LAW OFFICE OF MILLER & CURTIS
5489 Blair Road, 5th Floor
Dallas, TX 75231
Tel.: (214) 373-3761
Fax: (214) 987-2545
E-Mail: curtis@millerandcurtis.com

Attorneys for Plaintiff Helene Rush

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I. INTRODUCTION

It was never in defendants' financial interests to do the appropriate types of studies to measure the degree of breast cancer risk associated with combination menopausal hormone therapy ("CMHT"). It was more profitable to leave it to others to do the studies and to cloud the existing scientific knowledge. It is no different in litigation. Defendants use the same convenient distortions here to argue for the exclusion of Dr. Austin's testimony.

Dr. Austin is an esteemed epidemiologist whose previous ecological research on cancer trends helped lead to the consensus in the scientific community that Premarin increases the risk of endometrial cancer. Now he has completed a similar type of study based on data and statistical methods readily available to defendants. His opinion is clear and concise: By monitoring the publicly available SEER breast cancer registry data, defendants would have detected a signal in the 1980s that CMHT may be causing a disproportionate increase in hormone-dependent breast cancers. This signal should have motivated defendants to conduct case-control studies to confirm and quantify this effect.

Defendants attempt to muddy Dr. Austin's testimony by claiming that his focus on lobular cancers (which are virtually always hormone positive) has no relevance to plaintiffs' ductal tumors. This argument is unscientific and ignores the important fact that both plaintiffs' tumors were also hormone receptor positive; in other words, the hormones in CMHT made them grow. The SEER registry did not record hormone receptor positive tumors until 1990. However, after 1990, the incidence of hormone receptor positive tumors, both ductal and lobular, was consistently increased. Therefore, the relevance of Dr. Austin's focus on the most hormone sensitive type of tumor available for analysis is obvious.

Defendants also allege in boilerplate fashion that Dr. Austin's opinions are unreliable. However, these arguments lack merit. Defendants do not quarrel that the statistical methods he used were flawed or miscalculated. Dr. Austin's analysis is not novel. Epidemiologists routinely do ecological studies, and Dr. Austin's findings are consistent with at least two similar studies published in peer-reviewed journals. They reported a disproportionate increase in

hormone-receptor positive breast cancers in older women and identified hormone replacement therapy as the most likely cause. Accordingly, defendants' motion should be denied.

II. BACKGROUND

A. The Importance of Cancer Surveillance

When Wyeth brought Premarin to market in the 1940s – before FDA required extensive premarket testing of drugs – it had no idea what long-term effects exogenous estrogen had on women. Yet Wyeth successfully marketed Premarin as a fountain of youth and encouraged doctors to prescribe it to every postmenopausal woman. In 1975 and 1976, Wyeth got a wake-up call. Two epidemiological studies[1] and an ecological study co-authored by Dr. Austin,[2] published in the New England Journal of Medicine, revealed that Premarin profoundly increased women's risk of uterine cancer. The news was a blow to Wyeth, and it threatened to obliterate the company's enormously profitable franchise on the menopause market.

Wyeth redeemed its profits with a single study in 1980, which reported that adding progestin to estrogen would reduce the risk of endometrial hyperplasia.[3] The study was not designed to determine whether the addition of progestin would reduce the risk of endometrial *cancer.* But Wyeth and other defendants used the data to argue that a reduction in hormone-induced cellular proliferation (hyperplasia) was a valid biomarker for the reduction in the risk of uterine cancer. Progestin thus became Wyeth's Band-Aid for the cancerous wound caused by Premarin.

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[1] D.C. Smith et al., *Association of exogenous estrogen and endometrial carcinoma,* 293, No. 23, N. ENGL. J. MED. 1164-67 (Dec. 4, 1975); TM Mack et al., *Estrogens and endometrial cancer in a retirement community,* 294, No. 23 N. ENGL. J. MED. 1262-67 (Jun. 3, 1976).

[2] N. Weiss, D. Dzekely, & D. Austin, *Increasing incidence of endometrial cancer in the United States,* 294, No. 23 N. ENGL. J. MED. 1259-76 (Jun. 3, 1976).

[3] R. D. Gambrell et al., *Use of the progestogen challenge test to reduce the risk of endometrial cancer,* 55, No. 6, OBSTETRICS & GYNECOLOGY 732-38 (Jun. 1980).

As the self-proclaimed Leader in Women's Health, Wyeth should have been concerned about the potential for progestin, a synthetic progesterone, to cause breast cancers.[4] The endometrial cancer scare with Premarin should have been enough for Wyeth to begin doing preliminary studies to find out whether the *combination* hormone therapy regimen could be stimulating the growth of breast tumors in women using this regimen.

The quickest and most inexpensive way to generate this hypothesis was to monitor the SEER and HMO breast cancer registries for a signal, an increase in hormone sensitive tumor types in the postmenopausal women. Ecological studies were specifically designed for detecting signals for this purpose.[5] In addition, SEER and other breast cancer registries were free and readily accessible to Wyeth in the 1970s. Wyeth used the SEER database routinely in its marketing materials to measure the background rate of cancer.

Had the ecological data shown a disproportionate increase in hormone-dependent tumors, the next logical and reasonable step for Wyeth to take was to conduct two or three case-control studies – the standard epidemiological method to measure the increased risk of cancer in an exposed group of people compared to cancers in an unexposed group. Indeed, it was Dr. Austin's ecological study, combined with three case-control studies, that alarmed the medical community about the risk of estrogen-induced endometrial cancer and prompted the FDA to call for new labeling to restrict the use of menopausal estrogen to women with hysterectomies.

It was feasible for Wyeth to conduct and complete these ecological and case-control studies in the 1980s. By then, Wyeth would have a much clearer understanding that the combination of estrogen and progestin could cause a significantly higher risk of breast cancer than estrogen alone. Instead, the Leader in Women's Health remained incurious, choosing to

[4] Indeed, there were early red flags in the worldwide literature showing that CMHT may induce breast tumors in animals. M. Riviere, et al., *Appearance of mammary tumors in the male rat subjected to combined estrogen and progesterone treatment,* 155 C R SEANCES SOC. BIOL. FIL. 2102-04 (1961); Finkel & Berliner, *The extrapolation of experimental findings (animal to man): The dilemma of the systematically administered contraceptives,* 62nd Annual Meeting of the International Academy of Pathology (Feb. 28, 1973).

[5] Ecological studies gather and compare differences in disease rates among different populations.

bury its head in the sand. By doing nothing, Wyeth reaped a nearly 900% increase in Premarin sales between 1980 and 1990.[6]

At trial, Wyeth will claim that it did everything right, alleging there were no signals that hormone therapy could cause breast cancer, thus no need to do any studies. Wyeth will employ deceptions and obfuscations, pointing to estrogen studies, not combination studies to argue that the risk of breast cancer with its drug is weak, and that WHI showed nothing new. In anticipation, plaintiffs retained Donald Austin, M.D., MPH, and his colleague, David Buckley, M.D., to double-check Wyeth's story. By conducting an ecological study using well-established statistical methods and data available to Wyeth, Dr. Austin found that by the early 1980s, Wyeth could easily have detected a signal suggesting that CMHT may be causing a disproportionate number of hormone-dependent breast cancers. Based on that clear signal, Wyeth should have followed up with case-control studies.

B. Dr. Austin's Research

Dr. Austin is a physician and epidemiologist. He is a Professor in the Department of Public Health and Preventive Medicine at the Oregon Health & Science University in Portland, Oregon. Previously, he worked for 22 years for the California Department of Health Services, where he designed and operated cancer surveillance systems and used them for descriptive and analytic epidemiologic studies. Most important, Dr. Austin was one of the scientists who developed the SEER database. Dr. Austin has also been involved in national studies of cancers and their risk factors and has served on NIH peer review panels.

In particular, Dr. Austin conducted a study on endometrial cancer rates in the decade of the 1970s. His study showed that there was a new and disproportionately high occurrence of endometrial cancer in women over 50 years old and living in affluent areas. Dr. Austin's data were presented to the FDA, along with three case control studies showing that estrogen hormone replacement therapy was a strong risk factor for epidemiological cancers. These findings led the FDA to require new class labeling to warn of the risk. Afterwards, Dr. Austin published a

6 Ex. 01, LAWT-006-00913, Premarin family sales in dollars, 1942-2001.

follow-up study, which showed that the overall endometrial cancer incidence decreased following the FDA's action requiring new warnings for estrogen replacement therapy.[7] At that time, Dr. Austin was interesting in finding out whether estrogen was a promoter of cancers of women on hormone therapy. He even contacted a Wyeth sales representative to obtain Premarin sales and prescription data, in order to determine whether increased sales corresponded to an increase in cancers. Dr. Austin was told that Wyeth would not provide him the data[8] and that Wyeth considered him persona non grata.[9] To his knowledge, no one at Wyeth or elsewhere ever conducted such a study.

Plaintiffs retained Dr. Austin in this litigation to answer this question, among others: If the available national cancer data had been monitored for changes in breast cancer incidence, could an increase in invasive lobular cancer ("ILC") have been detected, and if so, when?[10] For his analysis, Dr. Austin used the National Cancer Institute's SEER database, because it was one of the earliest and most comprehensive publicly available sources of cancer information. Furthermore, Wyeth was already familiar with the SEER database. Dr. Austin selected ILC as the histological subtype to monitor, because SEER did not collect data on hormone receptor status until 1990.[11] The effect of a new hormonal exposure would only be expected to increase in a few estrogen sensitive breast cancer subtypes. ILC was the most logical cell type to examine because it is hormonally the most sensitive.[12]

The statistical models used by Drs. Austin and Buckley to measure the degree, if any, of any increase in proportion of ILCs from 1980 through 2000 are the same standard and widely accepted methodologies used by epidemiologists and statisticians to conduct similar ecological

[7] D. Austin & K. Roe, *The decreasing incidence of endometrial cancer: public health implications*, 72 AM. J. PUB. HEALTH 65-68 (Jan. 1982).

[8] Ex. 02, Austin dep. at 41

[9] Ex. 03, Austin dep. at 163

[10] Ex. 04, Austin report at i.

[11] Ex. 04, Austin report at 6.

[12] Ex. 04, Austin Report at 2.

studies – both now and in the 1980s. Dr Jody Lapidus, a biostatistician and professor at OHSU, validated the study design and verified the statistical formulae used to ensure that the methods used in the study were sound and appropriate.[13]

Using the methods described in his report, Dr. Austin's analysis found that the proportion of ILCs compared to all breast cancers was steadily increasing in SEER, but only among women age 50 and older. This effect was significantly detectable for the first time in 1981. For most of the following 20 years, the effect remained increased, often significantly, over baseline.[14] Furthermore, from 1990 (the first year that SEER recorded estrogen receptor positive cancers) through 1997, the proportion of *all* estrogen receptor positive tumors – both lobular and ductal – was elevated over other tumor types – although ILCs had the highest proportional increase.[15] By 1983 or 1984 at the latest, Wyeth should have been aware of this signal. While the data would not have established a causal relationship, it generated enough suspicion of causation to warrant further studies.

Well-designed case control studies were appropriate to measure the strength of the association and control for confounders or other risk factors. Case control studies are inexpensive and can be done quickly. To measure the risk in this instance, the investigator would recruit several hundred women with the breast cancer subtype of interest, as well as several hundred matching women in the control group. Researchers would then compare the past rate of CMHT use in both the case and control group. The study could achieve results within two to three years. Dr. Austin has designed and conducted several case control studies in his career. He estimates the cost to complete such a study in current dollars is less than $1.8 million.[16]

[13] Ex. 05, Buckley dep. at 29-32.

[14] Ex. 04, Austin report at vii.

[15] *Id.* at 15.

[16] Ex. 04, Austin report at Addendum.

III. LEGAL ARGUMENT

The Eighth Circuit has emphasized that nothing in *Daubert* or Rule 702 requires an expert to resolve an ultimate issue of fact to a scientific absolute in order to be admissible. *Kudabeck v. Kroger Co.,* 338 F.3d 856, 861 (8th Cir. 2003). It is the expert witnesses' methodology, not their conclusions, that is the primary concern of Rule 702. *Bonner v. ISP Technologies, Inc.,* 259 F.3d 924, 929 (8th Cir. 2001). A challenge to the factual basis of an expert's opinion goes to the credibility of the testimony, not the admissibility. *Marvin Lumber & Cedar Co. v. PPG Indus., Inc.*, 401 F.3d 901 (8th Cir. 2005). And to the extent that a party challenges the probative value of the evidence, an attack on the probative sufficiency of the evidence does not relate to admissibility but to the weight of the evidence and is a matter for the jury to resolve. *United States v. Beasley,* 102 F.3d 1440, 1451 (8th Cir. 1996).

A. Dr. Austin is Not Offering Opinions on Causation.

Defendants repeatedly contend that the ecological studies conducted by Dr. Austin do not prove that CMHT causes breast cancer, and therefore, his opinions are unreliable. The argument is a straw man offense. In his report and during his deposition, Dr. Austin repeatedly stressed that the purpose of his analysis was not to prove causation. That is not what ecological studies are designed to do. To the contrary, his research, like any good ecological study, was designed to identify signals, if any, that were suggestive of a cause, which in turn would generate follow-up studies. As Dr. Austin put it, these types of studies are "looking for signals of alarm that you want to follow up on."[17] Dr. Austin explained the value of an ecological study once it finds a change in cancer incidence rates:

> At any time there is a change in an incidence rate, it happens because of some reason. And that reason is usually identified as a cause. Now, if – and there are other things that have to be ruled out such as artifactual reasons, such as changes in reporting or changes in interpretation, et cetera, et cetera. But if that happens, then you have some concrete information about, here is an anomaly, what's causing it. And this is the population group that would be susceptible to A, B, C and D, and let's find out if that's the case. *It's a motivation to do something.*

[17] Ex. 06, Austin dep. at 36.

> *It's exactly the same kind of focus that leads to analytic studies, case control, Women's Health Initiative, cohort studies, et cetera.*[18]

Dr. Austin's testimony will help the jury understand the sources of information that were available to pharmaceutical companies like Wyeth as a first step to motivate them to find out the degree to which their drugs might be increasing the risk of long-term harm to the women using them. Dr. Austin is exceptionally well qualified to explain the importance of monitoring cancer registry databases for signals of harm. After all, his earlier work – which employed the same methodology – helped lead to the discovery that Premarin use increased the risk of endometrial cancer.

B. The Lobular Cancer Signal Identified by Dr. Austin Is Directly Relevant to the *Reeves* and *Rush* Cases.

Defendants argue that because Dr. Austin looked at lobular tumors and not ductal tumors, his research lacks "fit." It is precisely this confused short-sightedness that allowed defendants to remain willfully blind to the long suspected association between CMHT and breast cancer in the first place. Defendants misconstrue the science of hormones and their role in breast cancer.

The state of scientific knowledge has always been that if combining estrogen with a progestin were to influence cancers, it would most likely influence hormone dependent tumors. Dr. Austin observed this same phenomenon with unopposed estrogen and endometrial cancer in the early 1970s. But SEER did not begin recording estrogen-receptor (ER) or progesterone-receptor (PR) status on tumors until 1990, so it was not possible to monitor for increases in ER and PR positive breast cancers in that particular database during the 1980s. Nevertheless, it has long been known that some rarer subtypes reported in the SEER registry are virtually all 100% ER positive. The most common of these ER positive cancer subtypes is invasive lobular carcinoma (ILC). Thus, the most methodologically sound way to look for a signal that the new combination hormone therapy drug was increasing hormone dependent tumors was to track an increase in lobular cancers. If this research detected a signal, the next logical scientific step

[18] Ex. 07, Austin dep. at 54-55 (emphasis added).

would be to conduct case control studies measuring the incidence of all types of ER positive tumors in the exposed groups compared to non-exposed groups.

In fact, Dr. Austin's research did find an increase in all ER positive tumors – including ductal tumors – after 1990, when the SEER registry began recording ER positive data.[19] These findings are consistent with a similar ecological study by Glass and Hoover in 1990, which analyzed the Kaiser HMO cancer database.[20] Unlike SEER, the Kaiser registry recorded ER positive breast tumors. Looking specifically at receptor status for all histological tumor subtypes (lobular, ductal, and others), Glass and Hoover observed a sharp increase in ER positive breast cancers in women 60 or older. After the values were adjusted for age, the authors found that the incidence of cancers rich in estrogen receptors rose much faster than that of cancers that were receptor poor.[21] Confounding factors such as improved mammographic techniques or artifacts of cancer registration were unlikely to account for the increase.[22] The authors noted that hormonal influences may be responsible for the differential increase in ER positive breast cancer over time.[23] The Glass and Hoover study also supports the point that monitoring the incidence of ductal tumors (including both ER positive and ER negative subtypes) would dilute the breast cancer signal substantially, because only approximately 60% of ductal tumors are truly ER positive.[24]

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[19] Ex. 04, Austin report at 15.

[20] Ex. 08, Andrew G. Glass & Robert N. Hoover, *Rising Incidence of Breast Cancer: Relationship to Stage and Receptor Status*, 82, No. 8, J. NATIONAL CANCER INSTITUTE (1990). Bates No. HRT MED LIT 0192001-004.

[21] *Id.* at 0192004.

[22] *Id.*

[23] *Id.*

[24] T. Bagai & Shousha S., *Oestrogen receptor negativity as a marker for high-grade ductal carcinoma in situ of the breast,* 44, No. 5 HISTOPATHOLOGY 440-47 (May 2003); Li et al., *Clinical characteristics of different histologic types of breast cancer,* 93, No. 9 BR. J. CANCER 1046-52 (Oct. 31, 2005); A. Rody et al., *Estrogen receptor alpha and beta, progesterone receptor pS2 and HER-2/neu expression delineate different subgroups in ductal carcinoma in situ of the breast.* 12, No. 4, ONCOLOLOBY REP. 695-99 (Oct. 2004). *See also* REFERENCE MANUAL ON SCIENTIFIC EVIDENCE, p. 509 n. 96 (2004) (*quoting* Rothman & Greenland: "Unwarranted assurances of a lack of any group effect can easily emerge from studies in which a wide range of etiologically unrelated outcomes are grouped.")

Dr. Austin's analysis of ILC, a type of cancer known for its hormone receptor sensitivity, is not only scientifically appropriate, but it squarely fits the facts of this case. We know from internal company documents that Wyeth had access to, and looked at, the SEER breast cancer database. Based on Dr. Austin's work, followed by case control studies, Wyeth knew in the 1970s that Premarin, the estrogen component of hormone therapy, caused an increase in endometrial cancers. Wyeth also had cause for concern that the addition of progestin to estrogen might cause breast cancer. The appropriate first step for Wyeth was to monitor SEER for increases in the most hormonally sensitive breast cancers over time. Because SEER did not report ER and PR status, the most precise way of detecting possible hormonal influence was to track lobular cancers, which are always hormone receptor positive. Analyzing ductal tumors would not have been helpful because a significant percentage of ductal cancers are ER negative. Dr. Austin's study found that in the postmenopausal population of women, there was a statistically significant increase in the proportion of hormone dependent lobular tumors beginning in 1981. Further, once data on ER positive tumors became available in the 1990s, analysis of the SEER database showed that ER positive breast cancers also consistently increased during that period.[25]

Dr. Austin's research confirms that the CMHT breast cancer signal was there all along, if defendants were interested in looking for it. Those findings would have prompted a responsible pharmaceutical company to follow up with several case control studies to measure the effect of CMHT on all hormone receptive positive breast cancers. Ultimately, other independent researchers – not defendants – carried out these studies, which confirm that the signal found in Dr. Austin's work was real. His findings fit neatly with the facts in this case.

His study is all the more compelling because it shows more precisely that CMHT's effect on hormone dependent tumors provided an important signal of causation. Had Dr. Austin looked only at both ER positive and ER negative ductal tumors – as defendants insist he should have

[25] Ex. 09, Austin dep. at 21.

done – his methodology would be fatally flawed. It would have inappropriately grouped ER negative tumors, which are not influenced by hormones, together with ER positive ductal tumors, which are hormone sensitive. The results would have unreliably understated the increase in ER positive tumors.

Defendants are simply incorrect and misguided to claim that Dr. Austin's focus on lobular cancers is irrelevant. The analysis is directly relevant and is admissible to show what defendants could have done, but did not do, to answer serious long-term safety questions about CMHT. Defendants' inaction led to an unacceptable delay in current knowledge that CMHT causes hormone dependent breast cancers.

Defendants essentially dispute the probative sufficiency of the evidence. As the Eighth Circuit has held, such a dispute goes to the weight of the evidence, not its admissibility. *Beasely,* 102 F.3d at 1451; *Bonner,* 259 F.3d. at 929. This is a matter for the jury to decide.

C. Ecological Studies are Not Intended To Rule Out Other Risk Factors For Breast Cancer.

Defendants maintain that Dr. Austin's study is *per se* unreliable because it did not account for other risk factors or rule out other explanations for the increase in ILC. Again, defendants fail to understand the purpose of an ecological study, or for that matter, the purpose of Dr. Austin's testimony.

The REFERENCE MANUAL defines ecological studies this way:

> In contrast [to case control and cohort studies], studies that collect data only about the group as a whole are called ecological studies. In ecological studies, information about individuals is generally not gathered; instead, overall rates of disease or death for different groups are obtained and compared. The objective is to identify some difference between the two groups, such as diet, genetic makeup, or alcohol consumption that might explain differences in the risk of disease observed in the two groups. Such studies may be useful for identifying associations, but they rarely provide definitive causal answers.

REFERENCE MANUAL ON SCIENTIFIC EVIDENCE, at p.481. Ecological studies do not rule out an individual's exposure to other agents or risk factors that might also be responsible for breast cancer. Nevertheless, ecological studies are useful in that they identify an area for further

research. *Id.* Once a difference in disease rates is identified, it is appropriate to follow up with a study based on gathering data about individuals. *Id.*

The focus of Dr. Austin's research was to monitor the SEER data beginning in 1980 to look for signals of an increase in hormone-dependent breast cancers, using methods available to defendants. He found it. As Dr. Austin has stated repeatedly in his deposition testimony, the signal should have motivated defendants to do something, specifically, to follow up with case control studies to measure the effect and to rule out other competing theories for causation.

D. What Doctors Would Have Done with Information About CMHT's Effect on Breast Cancer Cell Types Is Irrelevant.

Defendants also complain that Dr. Austin's opinions are unreliable because there is no evidence that prescribing physicians would have paid any attention to a warning about the increased proportion of any breast cancer cell type in women over 50. This argument completely misses the point.

The relevance of Dr. Austin's research is not to prove that defendants failed to warn about the results of ecological studies, but rather, it put defendants on notice of the need to do the appropriate case control studies to determine whether CMHT put women at increased risk of breast cancer. Thus, the issue is what *defendants* should have done with the information, not what physicians would have done. Dr. Austin's testimony is directly relevant to defendants' duty to test their product to address safety issues, not defendants' failure to warn. Whether defendants did not adequately warn physicians about the risk of breast cancer, based on what they did or did not do to follow up on the ILC signal, is for a jury to decide.

E. Dr. Austin's Testimony Easily Meets *Daubert's* Criteria for Admissibility.

As the Supreme Court has noted, none of the criteria for admissibility should be taken as a definitive checklist. *Kumho Tire Co. v. Carmichael,* 526 U.S. 137, 141-42 (1999). "This evidentiary inquiry is meant to be flexible and fact specific, and a court should use, adapt, or reject *Daubert* factors as the particular case demands." *Unrein v. Timesavers,Inc.,* 394 F.3d 1008, 1011 (8th Cir. 2005).

Moreover, the trial court's role is not to decide whether an expert's opinion is correct. It is the expert's methodology, not his conclusions, that is the primary concern of Rule 702. *Bonner v. ISP Technologies, Inc.,* 259 F.3d 924, 929 (8th Cir. 2001); *Kudabeck v. Kroger Co.,* 338 F.3d 856, 929 (8th Cir. 2003). The factual basis of an expert's opinion goes to the credibility of the testimony, not the admissibility. *Marvin Lumber & Cedar Co. v. PPG Indus., Inc.,* 401 F.3d 901, 929 (8th Cir. 2005) (rejecting defendant's argument that expert's studies were done for litigation, sample size was too small, and failed to account for other factors).

Here, defendants misinterpret *Daubert* and Rule 702. For example, they claim that Dr. Austin's testimony is unreliable because his conclusions have not been published or subjected to peer review. The defendants fail to understand the clear directive of the Supreme Court and the Eighth Circuit that the focus of the reliability inquiry is methodology the expert employed, not his conclusions. As explained below, the methodology Dr. Austin used, and his application of it to the relevant facts, are undisputedly reliable and well accepted in the scientific community. Any dispute over the factual basis for Dr. Austin's analysis, or his conclusions, is up to the jury to decide.

1. Whether the theory can be or has been tested.

Dr. Austin undertook an ecological analysis of a cancer registry database to look for a differential change in hormonally sensitive breast tumors. Defendants' contention that no similar studies have been conducted is incorrect. Defendants overlook the ecological study published in 1990 by Glass and Hoover, which analyzed data from the Kaiser Permanente national cancer registry. The authors employed the same technique as Dr. Austin. Consistent with Dr. Austin's study, Glass and Hoover identified an increase in estrogen-receptor positive breast cancers in older women in the post-menopausal age group.[26] More recently, Dr. Li and colleagues at the University of Washington conducted an ecological study of the SEER database, just as Dr.

[26] Ex. 08, Glass & Hoover (1990). The authors cited to ecological studies of other cancer registries that reported similar findings.

Austin did. The Li study also found an increase in lobular cancers in women over 50.[27] The authors cited hormone replacement therapy as the most likely possible cause (after considering other possible explanations such as improvements in pathology reading, mammography screening, etc.), since the increase in HRT prescriptions over the past two decades has risen concomitantly with the rise in lobular cancers.[28] The Glass & Hoover and Li studies both confirm and validate the analysis done by Dr. Austin. And the fact that ecological studies on changes in breast cancer rates are routinely conducted demonstrates that the technique is readily testable and often repeated.

2. Peer review and publication.

Dr. Austin's study has not yet been submitted for publication. But that does not make his opinion unreliable. As the Supreme Court in *Daubert* emphasized, "[s]ome propositions, moreover, are too particular, too new, or of too limited interest to be published." *Daubert v. Merrell Dow Pharms., Inc.,* 509 U.S. 579, 593 (1993). And the Eighth Circuit has made clear that publication is not a prerequisite for admissibility of expert testimony. *Kudabeck,* 338 F.3d at 862; *Bonner,* 259 F.3d at 929; *Riley v. Target Corp.,* 2006 WL 1028773, at *5 (E.D. Ark. Apr. 13, 2006).

As discussed above, other studies similar in both methodology and conclusions have already been published in the peer-reviewed literature. This fact bolsters the reliability of Dr. Austin's study.

3. Known or potential rate of error.

In this context, the known or potential rate of error has more to do with the methods of statistical calculations than whether the study's method has been reproduced with different results. Other ecological studies on data from breast cancer registries have yielded results consistent with Dr. Austin's analysis. The results of these studies, as well as Dr. Austin's, were

[27] Ex. 10, C. Li et al., *Changing incidence rate of invasive lobular breast carcinoma among older women,* 88, No. 11, CANCER 2561-69 (Jun. 1, 2000).

[28] *Id.* at 2567.

statistically significant (95% confidence), which means that it was highly unlikely that the findings were due to error, such as false positives. Thus, there is nothing about Dr. Austin's research or underlying technique that suggests an unacceptable rate of error.

4. General Acceptance.

Defendants also declare that because Dr. Austin's opinions have not been expressed outside litigation, they could not be widely accepted. Defendants misquote the law. This criterion does not require the *opinion* to be widely held. It is the underlying technique that is at issue. This is what the Supreme Court actually stated when it addressed general acceptance the general acceptance factor:

> Widespread acceptance can be an important factor in ruling particular evidence admissible, and 'a known *technique* which has been able to attract only minimal support within the community,' may be properly viewed with skepticism.

Daubert, 509 U.S. at 594 (internal citations omitted) (emphasis added). Throughout its opinion, the Court emphatically stated that the focus on the inquiry should be on the principles and methodology the expert uses and not on the conclusions generated. *Id.*

Defendants have no reliable scientific basis to challenge the reliability of ecological studies. They are a generally accepted method for identifying changes in disease rates in populations.[29] Epidemiologists employ this technique routinely to look for possible explanations for different rates of disease or death in demographic groups. Other researchers have published findings similar to Dr. Austin's in the peer-reviewed literature. The scientific community has not criticized these studies or demanded that their results be revised or retracted. And more recent studies have confirmed the association between hormone receptor positive tumors and CMHT. Based on those studies, it is generally accepted in the scientific community that CMHT can cause breast cancer.

5. Whether the opinions were developed solely for litigation.

Defendants make much of the fact that Dr. Austin conducted his analysis for litigation. Plaintiffs find this attack on Dr. Austin disingenuous in light of the fact that defendants have

denied all along that there were any signals to put them on notice in the 1980s of the need to do case control studies to measure the risk of CMHT and breast cancer. Defendants' failure to monitor the SEER database in the first place led Dr. Austin to conduct his analysis.

Moreover, Dr. Austin has had a long-standing interest in hormone therapy and cancer. It was Dr. Austin who first investigated the potential relationship between estrogen therapy and endometrial cancer. His study, combined with case control studies, led to the discovery that Premarin was strongly associated with endometrial cancers.

Defendants failed to mention that, 25 years ago, Dr. Austin wanted to do more thorough surveillance to see if hormone therapy sales correlated with the increase in cancer rates in specific populations. When he approached a Wyeth regional sales representative to find out how to obtain Premarin sales and prescription data, Dr. Austin was told that he was "persona non grata" and that Wyeth was not interested in providing him the information.[30] Thus, years before this litigation started, Dr. Austin was suspicious that hormone therapy might be responsible for the increase in cancer in postmenopausal women.

F. Dr. Austin's Testimony Is Directly Relevant and Not Subject to Exclusion under Rule 403.

Dr. Austin's testimony is relevant to show what defendants have denied, both in litigation and throughout the history of their drugs: that it was feasible in the 1980s to see a signal that CMHT might be increasing the risk of hormone-dependent breast cancers in postmenopausal women, and that the signal warranted further studies to confirm the association. As explained above, this evidence meets the standards for reliability and relevance under *Daubert* and Rule 702.

All evidence used against a party is by nature prejudicial. However, Rule 403 requires that the prejudice be unfair. *U.S. v. Young,* 754 F. Supp. 739, 742 (D.S.D. 1990). Unfair prejudice means an undue tendency to suggest decision on an improper basis, commonly, though

(Cont.)

[29] Reference Manual on Scientific Evidence, at p. 481.

[30] Ex. 11, Austin dep. at 40-41, 163.

not necessarily, an emotional one. *Id.* It is not surprising that defendants seek to exclude Dr. Austin's testimony because it makes them look bad. However, that reason is not a proper basis for excluding the evidence, given the important probative value of Dr. Austin's testimony. There are no grounds to exclude it under Rule 403.

IV. CONCLUSION

Dr. Austin's opinions meet the *Daubert* threshold for admissibility. His testimony is relevant to the facts of the case. His research was based not on guesswork, as defendants callously charge, but on careful, generally accepted epidemiological methods. What defendants challenge are the factual bases for Dr. Austin's opinions. Under the Eighth Circuit, the factual basis of his opinions goes to the credibility of his testimony, not admissibility. For the reasons stated above, the Court should deny defendants' motion.

DATED: June 29, 2006.

Respectfully submitted,

By: /s/ Les Weisbrod

Les Weisbrod, Esq.
MORGAN & WEISBROD
11551 Forest Central Dr., Suite 300
P.O. Box 821329
Dallas, TX 75243
Tel: (214) 373-3761
Fax: (214) 739-4732

William B. Curtis, Esq.
LAW OFFICE OF MILLER & CURTIS
5489 Blair Road, 5th Floor
Dallas, TX 75231
Tel.: (214) 373-3761
Fax: (214) 987-2545
E-Mail: curtis@millerandcurtis.com

Attorneys for Plaintiffs

Plaintiffs' Liaison Counsel

Russell Marlin, Esq.
William Gary Hold, Esq.
GARY EUBANKS & ASSOCIATES
708 West Second Street

P.O. Box 3887
Little Rock, AR 72201

Co-Lead Counsel on Behalf Of Personal Injury Plaintiffs

Ms. Zoe Littlepage
LITTLEPAGE BOOTH
408 Westheimer Street
Houston, TX 77006
(713) 529-8000
(713) 529-8044 Facsimile

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CERTIFICATE OF SERVICE

I hereby certify that a copy of the foregoing document was served according to this Court's provision for service as set forth in the pretrial orders and sent to the following counsel of record as indicated below on this 29th day of June, 2006.

By: /s/ Les Weisbrod
Les Weisbrod

VIA ECF AND E-MAIL

Ms. Lynn Pruitt
Mitchell Williams Selig, Gates & Woodyard
425 West Capitol, Suite 1800
Little Rock, Arkansas 72201

DEFENDANTS' LIAISON COUNSEL

VIA ECF AND SERVICE THROUGH LIAISON COUNSEL
TO THE FOLLOWING COUNSEL

John W. Vanderman: jvardaman@wc.com
F. Lane Heard: lheard@wc.com
Stephen Urbanczyk: surbanczyk@wc.com
Williams & Connolly, LLP
725 12th Street NW
Washington, D.C. 20005
NATIONAL COUNSEL FOR WYETH DEFENDANTS

Jane E. Bockus.: snl@ctw.com
Clark Thomas & Winters
McCombs Plaza, Suite 165
755 East Mulberry
San Antonio, TX 78212
COUNSEL FOR DEFENDANT WYETH

EXHIBIT LIST

Exhibit	1.	LAWT-006-00913, Premarin family sales in dollars, 1942-2001.	SCO*
Exhibit	2.	Donald F. Austin, MD dep. at 41 (March 31, 2006)	
Exhibit	3.	Donald F. Austin, MD dep. at 163 (March 31, 2006)	
Exhibit	4.	Austin & Buckley Report (May 12, 2006)	
Exhibit	5.	David I. Buckley, MD dep. at 29-32. (March 27, 2006)	
Exhibit	6.	Donald F. Austin, MD dep. at 36 (March 31, 2006)	
Exhibit	7.	Donald F. Austin, MD dep. at 54-55 (March 31, 2006)	
Exhibit	8.	Andrew G. Glass & Robert N. Hoover, *Rising Incidence of Breast Cancer: Relationship to Stage and Receptor Status*, 82, No. 8, J. NATIONAL CANCER INSTITUTE (1990)	
Exhibit	9.	Donald F. Austin, MD dep. at 21 (March 31, 2006)	
Exhibit	10.	C. Li et al., *Changing incidence rate of invasive lobular breast carcinoma among older women,* 88, No. 11, CANCER 2561-69 (Jun. 1, 2000)	
Exhibit	11.	Donald F. Austin, MD dep. at 40-41, 163. (March 31, 2006)	

* Subject to Confidentiality Order (Filed Under Separate Cover)